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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,663	10/27/2006	Geert Verreck	PRD-2106-USPCT1	8190

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,663	VERRECK ET AL.	
	Examiner	Art Unit	
	Thurman Wheeler	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, and 9* is/are rejected.

7)☒ Claim(s) *7 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9 are pending in this application

Priority

Application 10571663 filed on 27 Oct 2006 is 10571663, filed 10/27/2006 is a national stage entry of PCT/EP04/52104, International Filing Date: 09/09/2004. PCT/EP04/52104 claims Priority from Provisional Application 60501639, filed 09/10/2003. Claims 1-9 of instant application 10571663 are supported by specification from said provisional application 60501639 filed on 09/10/2003.

Summary of Applicant's Claimed Invention

The aim was to investigate the combined possibilities of supercritical fluids (carbon dioxide) and hot melt extrusion of pharmaceutically acceptable polymers. Furthermore, injecting a pressurized gas as plasticizer for the polymer was investigated, and the ability to form a foam upon expansion of the pressurized gas. Also, particles of the polymer PVP-VA-64 or the polymer Eudragit-E100-PO, characterized in that said particles are shaped as platelets. Furthermore, said particles comprising the polymer PVP-VA-60 or the polymer Eudragit-E100-PO having an active ingredient, wherein the active ingredient is itraconazole.

Claim Objections

In claim 7, applicant claims pharmaceutical dosage form comprising a therapeutically effective amount of particles as defined in claims 4 to 6. And, in claim 8, a process of preparing a pharmaceutical dosage form as defined in claim 7
comprising the steps of intimately mixing particles as defined in claims 4 to 6 with pharmaceutically acceptable excipients and making from the thus obtained mixture a pharmaceutical dosage form comprising a therapeutically effective amount of particles. Thus, claims 7 and 8 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

Accordingly, claims 7 and 8 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "PVP-VA 60" is used by applicant to mean "PVP-VA 64". PVP-VA 64 (p.11, lines 5-10, 25-29;

p.12, 1-10; p.16, 2.1.1, lines 3-5; pgs. 29, 30, 33-36, 38-46. 48-56, 59, 60, 63, and 64-66) has been replaced by "PVP-VA 60" in claims 1-9 and in specification: p.12, lines 10-20, while the actual meaning of "PVP-VA 60" according to the context in which it is used is interpreted to be "PVP-VA 64". Thus, the term "PVP-VA 60' is indefinite because the specification does not clearly redefine the term.

Furthermore, in claims 1-6 and 9 the term 'platelets" is a relative term which renders the claims indefinite. The term "platelet" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant describes platelets as minute flattened particles, i.e. particles of which the thickness is smaller than the length and width (p.12, lines 12-14). To further complicate the subject matter applicant uses the term "minute", which is also an indefinite term that can be interpreted in varied degrees of relative size and proportion. Thus, according to applicant any small particle with a thickness smaller than its length or width is considered a platelet. Consequently, any particle not having equal sides as in a cube or diameter as in a sphere, would qualify as a "platelet" according to applicant. Therefore, the broadest reasonable interpretation of minute platelets is any relatively small particulate matter that is not a perfect sphere or a cube. In claim 3, applicant claims particles of the polymer Eudragit-E100-PO according to claim 1 wherein less than 40% (w/w) is smaller than 100 , where is the 12th letter of the Greek alphabet that is used in measurement as the SI prefix for micro, which represents one millionth or 10^{-6}. However, applicant does not indicate, specifically, to what unit the applies; e.g. m, which would indicate a micrometer or one millionth of a

meter. Therefore, without knowing the unit of which applicant refers to in claim 3 the subject matter in claim 3 is indefinite.

Claim rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Instant Claims 1 and 2 are rejected under under 35 U.S.C. 102(b) as anticipated by Kolter *et al* "Structure and Dry Binding Activity of Different Polymers, Including Kollidon VA 64", Drug development and Industrial Pharmacy, 26(11), 1159-1165 (2000) as evidenced by Verreck, G. *et al* "The effect of pressurized carbon dioxide as a plasticizer and foaming agent on the hot melt extrusion process and extrudate properties of pharmaceutical polymers"; J. of Supercritical Fluids 38 (2006) 383-391.

In claim 1, applicant claims particles of the polymer PVP-VA-64 or the polymer Eudragit-E100-PO, characterized in that said particles are shaped as platelets.

Accordingly, Kolter teaches PVP-VA-64 particulate binder material that has shell like structure (Fig.3), as described above. In claim 2, applicant claims particles of the polymer PVP-VA-64 according to claim 1 wherein the specific surface area is larger than 0.350 m^2/g.

In claim 2, applicant claims particles of the polymer PVP-VA-64 according to claim 1 wherein the specific surface area is larger than 0.350 m2/g.

Accordingly, the Verreck reference teaches specific surface area for PVP VA 64 as 196 m^2/kg. Thus, Kolter provides the guidance to obtain the PVP VA 64 particles having platelet shaped characteristics as applicant claims in claim 1. By the nature of the PVP VA 64 particles themselves they inherently have specific surface area of 196 m^2/kg, regardless of whether they are taught by the Kolter reference. The Verreck reference further teaches the specific surface area of 0.482 m^2/g for PVP VA 64 particles after carbon dioxide treatment, that is larger than the specific surface area of 0.350 m^2/g as claimed by applicant in claim 2 (p. 388, Fig. 3). Importantly, in specification applicant states, to be able to build up pressure in the extruder and dissolve the carbon dioxide into the polymeric carrier, the initial experiments focused on the extruder set up and optimisation of the screw configuration. For these experiments, PVP-VA 64 was used as a model polymer. Therefore, different screw configurations and extruder set ups were tested and evaluated (p. 11, Section II. Summary of Invention, lines 25-29). Thus, PVP VA particles have specific surface area of 0.482 m^2/g after treatment with carbon dioxide.

Thus, the Kolter reference discloses all of the limitations of PVP-VA-64 as claimed by applicant. Therefore, it follows that the particles as claimed by applicant in claim 2 are anticipated by the Kolter reference.

Instant Claims 4, 5, and 6 is rejected under 35 U.S.C. 102(b) as anticipated by Six *et al* "Thermal Properties of Hot-Stage Extrudates of Itraconazole and Eudragit E100Kolter", Journal of Thermal Analysis and Calorimetry, Vol. 68, (May, 2002) 591-601.

In claim 4, applicant claims particles comprising the polymer PVP-VA-60 or the polymer Eudragit-E100-PO, and an active ingredient, characterized in that said particles are shaped as platelets. Accordingly, Six teaches the preparation of physical mixtures by mixing itraconazole and eudragit E100 in a mortar for 5 min and sieved (355 micrometers). Powdered extrudates and physical mixtures containing 200 mg itraconazole or pure glassy itraconazole was added to the dissolution medium with a particle size smaller than 355 micrometer (p. 594, paragraphs 3 and 4). Thus, all the limitations in claim 4 are disclosed in the Six reference. Therefore, it follows that the subject matter in claim 4 is anticipated from the teachings of the Six.

In claim 5, applicant claims particles according to claim 4 wherein the active ingredient is itraconazole. Accordingly, Six teaches particles smaller than 355 micrometers composed of Eudragit E100 itraconazole, as described above. Furthermore, Six states The aim of the present study was to investigate the physical properties of solid dispersions of itraconazole and eudragit E100, prepared by hot-stage extrusion (page 592, paragraph 3). Thus, all the limitations in claim 5 are disclosed in the Six reference. Therefore, it follows that the subject matter in claim 5 is anticipated from the teachings of the Six.

In claim 6, applicant claims particles according to claim 5 wherein the weight by weight ratio of itraconazole to polymer ranges from about 10/90 to about 40/60. Accordingly, Six teaches itraconazole as a one phase system consisting of a molecular dispersion of the drug in eudragit E100 at concentrations below about 13% mass/mass when extrusion at 453.0 K. Furthermore, a two-phase system containing a drug load of more than 13% mass/mass consisting of a molecular dispersion of itraconazole in eudragit E100 and a phase consisting of pure itraconazole showing its characteristic liquid crystalline structure frozen into the glassy state at 413.0 K. The second phase consists of pure crystalline itraconazole. Unmilled dispersions extruded at 453.0 K with a drug load of 60% mass/mass or more showed cold crystallization into a polymorphic modification of itraconazole, which recrystallized into the stable crystalline modification upon further heating (p.600, third paragraph).
Thus, all the limitations in claim 5 are disclosed in the Six reference. Therefore, it follows that the subject matter in claim 6 is anticipated from the teachings of the Six.

Instant Claims 1 and 3 are rejected under 35 U.S.C. 102(a) as anticipated by over Eerikainen, H.; Preparation of polymeric nanoparticles containing corticosteroid by a novel aerosol flow reactor method; International Journal of Pharmaceutics 263 (2003) 69-83.

In claim 1, applicant claims particles of the polymer PVP-VA-64 or the polymer Eudragit-E100-PO, characterized in that said particles are shaped as platelets.

Accordingly, the Eerikainen reference describes particles as being spherical with smooth surfaces. However, the nanoparticles as illustrated in Fig. 4 (page 76) show a distribution of

particle shapes, some of which are spherically shaped while others are oblonged or non-spherical shaped particles, which would definitely fit within the descriptive range of applicant's conceptual description of platelets (Instant application: p.12, lines 12-14). Since the claim recites the term "characterized" which is considered open ended, the mixture of particles taught by Eerikainen et al., some of which are shaped as platelets anticipates claim 1.

In claim 3, applicant claims particles of the polymer Eudragit-E100-PO according to claim 1 wherein less than 40% (w/w) is smaller than 100 .

Accordingly, Eerikainen teaches Eudragit E 100 nanoparticles having a geometric number mean valve of 90 nanometer or 0.09×10^{-6} m or 0.09 m or .09 microns (Abstract, p.69; p.74 fig. 2), where said particles fit within the descriptive range of applicant's conceptual description of platelets, as described above. Thus, the Eerikainen reference teaches Eudragit E 100 particles that can be described as platelets and are smaller than 100 micrometers (Examiner has interpreted applicant's use of the symbol ' ' to mean micrometer). Thus, claim 3 is anticipated also.

Claim rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Instant claim 9 is rejected under 35 U.S. C. 103(a) as being unpatentable over Breitenbach (US Patent Number 6318650, published 20 Nov 2001) in view of Clark (WO/2003/057197).

In claim 9, applicant claims a process of preparing particles as defined in claim 1 or claim 4 comprising the steps of feeding the polymer, or a mixture of the polymer and the active ingredient, into a melt extruder, transporting the polymer, or a mixture of the polymer and the active ingredient, through the barrel of the melt extruder by means of a screw modified with transport elements and with kneading elements, -injecting pressurized gas into the barrel of the melt extruder through a port located in the barrel, mixing the polymer, or a mixture of the polymer and the active ingredient, and the pressurized gas under subcritical or supercritical conditions expanding the polymer, or a mixture of the polymer and the active ingredient, after the die plate, and milling the extrudate, characterized by creating a melt seal before the site of the pressurized gas injection by placing a reversing transport element in the screw configuration at said site.

Accordingly, Breitenbach teaches a process for the continuous production of solid, particulate preparations of bioactive substances, in which the bioactive substances are homogeneously dispersed in a matrix of thermoplastic auxiliaries, in a screw extruder having an extruder jacket, wherein the process comprises firstly melting the matrix auxiliaries and mixing the bioactive components with the matrix auxiliaries in a heatable zone of the extruder to form a mixture, and subsequently cooling, precomminuting and finely grinding the mixture in a cooling zone of the extruder to form a powder, wherein the screw geometry in the cooling zone is selected so that the cooling zone has a conveying zone, followed by a mixing zone and/or a

kneading zone (claim 1). Furthermore, the extruder jacket of the conveying zone of the cooling zone is cooled to a temperature which is 5 to 30 degree celsius below the softening temperature of the mixture (claim 2). The cooling zone has a conveying zone followed in the direction of flow by a mixing zone and then a kneading zone (claim 3). The extruder jacket of the mixing zone and/or the kneading zone in the cooling zone is cooled to temperatures in the range from -10 to +10 degree celsius (claim 4). Next, a blowing agent is added in the heating zone after the components of the mixture have melted (claim 5). A release agent is added to the mixture (claim 6). Wherein, the cooling zone is followed by a conveying zone having conveying elements to discharge the powder from the extruder, where the conveying elements project out of the screw channel by 0.5 to 1.5 times the screw diameter. In example 9 (p. col. 10, lines 60-67), the Breitenbach reference teaches Kollidon VA 64 was extruded in a twin-screw extruder with an output of 5 kg/h.

However, the Breitenbach reference does not specifically teach the pressurized gas under subcritical or supercritical conditions expanding the polymer as applicant claims in claim 9.

Accordingly, Clark teaches the production of microcellular foams that is typically carried out by injecting a supercritical fluid, for example carbon dioxide, into a polymer while the polymer is maintained under an elevated pressure. Where a supercritical fluid is defined as a material maintained at a temperature exceeding a critical temperature and at a pressure exceeding a critical pressure so that the material is in a fluid state in which it exhibits properties of both a gas and a liquid. The supercritical fluid and the polymer form a single-phase solution. The pressure acting on the solution is then rapidly reduced, resulting in controlled nucleation a very large number of nucleation sites. The gas then forms bubbles, the growth of which is controlled

by carefully controlling pressure and temperature (p.3, para 3). The polymer/supercritical fluid solution is produced continuously nitrogen, into the molten polymer in the barrel 36 of the injection delivered is preferably metered either by using a positive displacement pressure of the supercritical fluid as it passes through a porous metered supercritical fluid is then delivered to the extrusion barrel to form a single phase polymer/supercritical fluid mixture (p.6 para 5). Whereas, for purposes herein representative examples of thermoplastic polymers suitable for pharmaceutical applications include, polyvinylpyrrolidone/vinyl acetate (PVP/VA) (60:40) manufactured by BASF KOLLIDON VA 64; and polyacrylates and its derivatives such as the Eudragit family of polymers (p.9, para. 6).

Now, the process that Breitenbach teaches of a continuous production of solid bioactive substances in a screw extruder in view of the teachings provided by Clark form a process for the production of Kollidon 64 or Eudragit E100 polymeric materials containing pharmacologically active agents using supercritical fluids (SCF). This process as described by the combination of the Breitenbach and Clark references will maintain homogeneity of the product on cooling of the melts, which is a common problem associated with melt extrusion processes, in a straight forward manner.

Thus, there is strong motivation to combine the teachings of Breitenbach and Clark to provide a process using SCF to manufacture polymers containing therapeutic agents to provide an improved method to maintain homogeneity of the product. It follows that it would have been *prima facie* obvious to one skilled in the art, at the time of the invention was made, to have developed a process as applicant claims in claim 9.

Conclusions

Claims 7 and 8 are objected to, and claims 1-6, and 9 are rejected.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thurman Wheeler whose telephone number is (571)270-1307. The examiner can normally be reached on Monday - Thursday, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Patrick Nolan can be reached on (571)272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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